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LUNG FUNCTION AND ITS GROWTH

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16. ABSTRACT

Evidence that certain uncomplicated upper respiratory infections (URI) induce pulmonary function abnormalities in adults prompted a study in children where such infections occur more frequently. In a longitudinal study, 55 chilren aged 2.5 - 9 years were observed for a mean duration of 2 years. Spirometry and lung volume studies were obtained routinely every 3 months, with each URI and 4 weeks post-illness providing data on 636 well and 260 illness observations. Adjusted mean values of forced vital capacity (FVC), 1 sec forced expiratory volume (FEV_1), peak expiratory flow rate (PEFR), mid-maximal expiratory flow rate (MMEF) and expiratory flow rate at 50% FVC (V_{50}) decreased during URI. The data suggest lower respiratory tract involvement without signs or symptoms of lower airways or alveolar disease occurs with URI of varied etiology in childhood.

Respiratory Syncytial virus is the most common cause of severe lower respiratory illness in infants and recurrent infections occur commonly. To evaluate the immune response to primary and secondary RSV infection serial determinations of serum neutralizing antibody and circulating antigen reactive lymphocytes were performed. Although a brisk serum antibody response was seen after both infections, antigen reactive lymphocytes were only detected after the second episode.

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LUNG FUNCTION AND ITS GROWTH

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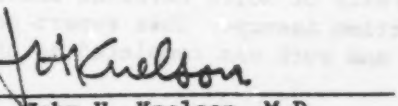
This report has been reviewed by the Health Effects Research Laboratory, U.S. Environmental Protection Agency, and approved for publication. Approval does not signify that the contents necessarily reflect the views and policies of the U.S. Environmental Protection Agency, nor does mention of trade names or commercial products constitute endorsement or recommendation for use.

FOREWORD

The many benefits of our modern, developing, industrial society are accompanied by certain hazards. Careful assessment of the relative risk of existing and new manmade environmental hazards is necessary for the establishment of sound regulatory policy. These regulations serve to enhance the quality of our environment in order to promote the public health and welfare and the productive capacity of our Nation's population.

The Health Effects Research Laboratory, Research Triangle Park, conducts a coordinated environmental health research program in toxicology, epidemiology, and clinical studies using human volunteer subjects. These studies address problems in air pollution, nonionizing radiation, environmental carcinogenesis, and the toxicology of pesticides as well as other chemical pollutants. The Laboratory develops and revises air quality criteria documents on pollutants for which national ambient air quality standards exist or are proposed, provides the data for registration of new pesticides or proposed suspension of those already in use, conducts research on hazardous and toxic materials, and is preparing the health basis for nonionizaing radiation standards. Direct support to the regulatory function of the Agency is provided in the form of expert testimony and preparation of affidavits as well as expert advice to the Administrator to assure the adequacy of health care and surveillance of persons having suffered imminent and substantial endangerment of their health.

This study provides baseline pulmonary function data on children living in an area of low environmental pollution. Children are studied longitudinally to characterize pulmonary function changes associated with physical growth and documented upper respiratory infections. This information will enable the design of further studies to assess the growth of lung function.



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ABSTRACT

Recent evidence that certain uncomplicated upper respiratory infections (URI) induce pulmonary function abnormalities in adults prompted a prospective study in children where such infections occur more frequently. In a longitudinal study, 55 children aged 2.5 - 9 years were observed for a mean duration of 2 years. Spirometry and lung volume studies were obtained routinely every 3 months, with each URI and 4 weeks post-illness, providing data on 636 well and 260 illness observations. After grouping of data by sex and age (< or > 84 mos), each spirometric parameter was analyzed using linear regression with individual identification, height, and clinical status (normal/URI) as independent variables. Adjusted mean values of forced vital capacity (FVC), one-second forced expiratory volume (FEV_1), peak expiratory flow rate (PEFR), midmaximal expiratory flow rate (MMEF) and expiratory flow rate at 50 percent FVC ($\dot{V}_{50}$) all decreased during URI; 35 percent of these changes were significant with $P \leq 0.05$ and 60 percent with $P \leq 0.1$. The data suggest that lower respiratory tract involvement without signs or symptoms of lower airways or alveolar disease occurs with URI of varied etiology in childhood.

The most prevelant respiratory infectious agent of early childhood causing both upper and lower respiratory infections is the respiratory syncytial virus. With evidence that RSV may cause repeated infections in children, studies of the immune responsiveness to recurrent RSV infections were initiated in the longitudinal population. Following each of two documented infections, most children developed an elevation of serum virus neutralizing antibody titer but less than 50% of children possessed detectable circulating antigen responsive T lymphocytes even after the second infection. These findings raise doubt as to the significance of cell-mediated immunity in disease pathogenesis and support the need to investigate other areas of the immune system such as local antibody responses to explain the recurrent nature of infections.

This final report was submitted in fulfillment of Grant R802233 by the University of North Carolina under the sponsorship of the U.S. Environmental Protection Agency. This report covers the period June 1, 1973 to July 31, 1976, and work was completed as of July 31, 1976.

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LIST OF ABBREVIATIONS

CMI	-- cell-mediated immune response
CO	-- carbon monoxide
FEV_1	-- forced expiratory volume (one second)
FRC	-- functional residual capacity
FVC	-- forced vital capacity
He	-- helium
$He-O_2$	-- helium - oxygen gas mixture
Hz	-- hertz (cycles per second)
ml/s	-- milliliters per second
MMEF	-- midmaximal expiratory flow (rate)
PEFR	-- peak expiratory flow rate
RSV	-- respiratory syncytial virus
SEBC	-- standard error between children
SEE	-- standard error of the estimates
TLC	-- total lung capacity
URI	-- upper respiratory infection
$\dot{V}_{50}$	-- vital capacity 50 percent ($\dot{V}_{25}$ -- 25 percent, etc.)

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SECTION 1

INTRODUCTION

There is increasing evidence that upper respiratory infections (URI) can induce pulmonary function abnormalities generally attributed to alterations in the lower airways. Picken et al. (1) first reported frequency dependence of dynamic compliance 4 to 8 weeks after a URI in otherwise normal subjects. With mild viral infections, others have described a decrease in CO-diffusing capacity (2), an increase in closing volume in smokers (3), a decrease in maximal expiratory flow rates with $He-O_2$ gas mixture at low lung volumes (3), and an increase in the frequency dependence of resistance in the range of 3 to 9 hertz (4). Blair et al. (5) also found an increase incidence of frequency dependent dynamic compliance with induced rhinovirus respiratory tract infections. In all instances several other measures of pulmonary function including spirometry were unchanged. Studies using nasally administered live attenuated influenza A vaccine showed small but consistent decreases in flow rates at low lung volumes (which were not observed after the second exposure) (6) and a decrease in the one-second forced expiratory volume (7).

In general, changes associated with URI are suggestive of peripheral airway obstruction. This is further supported by the fact that pulmonary function abnormalities seem to be more pronounced in smokers (2,3) and in patients with chronic obstructive respiratory diseases (7). These more pronounced effects are attributed to the superposition of two disease processes which compromise the small airways thereby causing significant decreases in effective airway radius with a much larger change in resistance. Hogg (8) has provided some evidence that a sharp increase in small airway conductance occurs around age four to five years; thus, in younger children small compromises in airway diameter may produce a marked effect on resistance, providing a situation similar to the adult subject with established disease. To further clarify this point we undertook a longitudinal study using small children in whom spontaneous upper respiratory infections are very common.

A secondary objective of the study was to obtain regression equations for predicting normal pulmonary function parameter values in children. There are consideralbe data for children older than six or seven years of age (9-12), but there is a paucity of data for younger children. Because of the longitudinal nature of our study we were able to train younger children and obtain sufficiently reproducible data to establish predictive equations.

SECTION 2

CONCLUSIONS

The results of these studies on immune responsiveness and Lung growth, as measured by pulmonary function testing in a longitudinal population of children in an area of low environmental pollution, have demonstrated:

1. The feasibility of obtaining reproducible pulmonary function test results in small children down to the age of three years.

2. The presence of upper respiratory tract infections at the time of pulmonary function testing in young children may alter the test results.

3. Cell-mediated immune responsiveness plays a minimal role in pathogenesis of illness accompanying respiratory syncytial virus infections in young children.

SECTION 3

RECOMMENDATIONS

1. In studies examining the effects of environmental pollution on pulmonary function in children it is imperative that the children be free of respiratory tract infections at the time of testing.

2. Methods should be developed to perform pulmonary function testing on children below three years of age in order to evaluate the effects of pollution on the lungs during this period of rapid development.

3. More information is needed on the immunological response of the respiratory tract in order that the effects of pollution on defense mechanisms may be better evaluated.

SECTION 4

METHODS

Subjects were 55 normal children (2.5 - 12 years old) who were studied longitudinally in a program previously described (13). Informed consent was obtained from the parents, and older children were informed of the value and intent of the study. Duration in the pulmonary-function study ranged from one to four years with a mean observation period of two years. Before being incorporated into the study, all children were thoroughly trained in pulmonary function maneuvers. Spirometry and the measurement of static lung volumes were performed on a scheduled basis every three months, at the onset of every respiratory infection, with the development of any complications, and at one month after the onset of illness.

Spirometry was performed in a standing position using a 10-liter wedge spirometer (Med. Science, Model 465). The flow signal was sampled 80 times per second, and stored in a Digital Equipment Corp. PDP-12/40. The digitized flow signal was integrated numerically to provide a volume signal. These data were analyzed using the program of Domizi, Earle and associates (14,15) to obtain forced vital capacity (FVC), one-second forced expiratory volume (FEV_1), peak expiratory flow rate (PEFR), midmaximum expiratory flow rate (MMEF), flow rate with 50 and 25 percent of the vital capacity remaining ($\dot{V}_{50}$ and $\dot{V}_{25}$). The spirogram, the flow-volume curve, and the computed pulmonary function parameters were displayed immediately for evaluation of technical perfection. Results of repeated trials and of previous test session were compared to insure a representative maximum effort. Flow and volume signals obtained on that day were stored on computer tape in the PDP-12/40 computer. Electronic calibrations were performed before each test. A one-liter syringe was used to calibrate the system weekly, and the flow signal was calibrated periodically with a rotometer.

Static lung volumes were measured in the seated position using helium dilution with the water-sealed spirometer (Collins nine-liter respirometer), modified to diminish dead space, and a helium (He) analyzer (Collins, helium meter). The volume of the system was maintained constant by addition of oxygen. No correction was made for absorption of helium. After three minutes, a maximum inspiratory effort was performed and the final He concentration measured. Functional residual capacity (FRC) and total lung capacity (TLC) were calculated. Generally, the child's mouth was held to the spirometer mouthpiece to avoid leaks, and if a leak was detected the entire procedure was repeated. These data were punched on computer cards and entered into the data file.

In addition to pulmonary function data, sitting and standing height, weight, age and clinical findings were also entered. The last included coding for: no disease; rhinitis; sore throat, sneeze, cough or earache; fever; asthma; pneumonia; and bronchiolitis.

During the analysis, data sets entered with findings of asthma, pneumonia and bronchiolitis (9 cases) and data from subjects with a history of asthma (3 subjects) were excluded. The data were further refined by eliminating all sets of pulmonary function data in which FEV_1/FVC was less than 0.7, or if $\dot{V}_{50}$ was less than $\dot{V}_{25}$ (less than four percent of observations). Remaining data were divided in four groups by sex and age with a separation at 84 months. The data were processed on the IBM 370/165 using SAS (18), to fit the variation in each pulmonary function parameter with a linear model. Age in months, individual identification and clinical status (asymptomatic or symptomatic) were used as independent variables. The analysis was repeated using height instead of age as an independent variable and again using both variables. The population means, the standard error of the estimate (SEE) and the standard error between children (SEBC) were calculated for each parameter in the four age-sex groups. Differences between asymptomatic and symptomatic subjects were evaluated by computing adjusted means for each parameter in these two subgroups within the four age-sex groups; F and P values were computed for intergroup comparisons.

SECTION 5

RESULTS

The study included 896 observations, of which 260 were obtained during expisodes of URI. In this section results of the regression analysis are presented first and then used to evaluate the effect of URI on pulmonary function parameters. Using both age and height as independent variables in the regression analysis produced the smallest SEE and SEBC. Generally, using height without age caused a small increase in these measures of variability, while using age without height produced a larger increase. This is illustrated by Table 1 which shows the SEE for FVC for the four age-sex groups computed for these three combinations of independent variables. This indicates that including age as an independent variable contributes little to the fit between the regression equation and the data because age and height are so closely related. As a result of this, the remainder of the results were derived using regression analyses that did not include age.

Regression equation coefficents for the eight pulmonary function parameters for the four age-sex groups are shown in Table 2. Slope values indicate lung function development relative to overall growth. For example, in males who were less than 84 months old, FVC increased 35.0 ml/cm of growth, while in females of the same age the corresponding value was 31.0 ml/cm. Comparing slopes in the two male age groups showed that five of eight were in the younger group; in contrast, all slopes in the older female group were greater or equal to those in younger females. When the comparison is made between sex groups, in the younger subjects, seven of eight slopes are greater in males while in the older population six of eight are greater in females. Thus in comparison to overall growth, lung function appeared to develop more rapidly in our younger male and older female subjects.

Tables 3 shows mean values, SEE and SEBC derived from the regression analysis of the eight parameters for each age-sex group. The SEE's define confidence limits on parameter values predicted from the regression equations for subjects in the population studied. Typical values are 100 to 200 ml for volume measurements (FVC, FEV_1, FRC and TLC) and 300 to 500 milliliters per second (ml/s) for flow measurements. These values provide a measure of the variability in repeated measurements in the same subject. The SEBC's define confidence limits on predicted values derived from the regression equation for the general population. These values are typically 50 to 150 ml or ml/s greater than the corresponding values for the SEE.

From the regression analysis, adjusted mean values for well subjects and for those with URI were computed and are shown in Table 4. This table also shows the statistical significance (F and P values) of the differences

between these two groups. In the symptomatic subjects the adjusted mean values of the spirometric parameters FVC, FEV_1, PEFR, MMEF and $\dot{V}_{50}$ show a decrease for all four age-sex groups. For FVC and PEFR, the difference was significant ($P \leq 0.1$) in three groups; for FEV_1 and MMEF, the difference was significant in two of the four groups, and for $\dot{V}_{50}$ the difference was significant in only one group. With $P \leq 0.05$, 35 percent of the changes were significant. Typically, the differences are 50 ml or ml/s for FVC, MMEF and $\dot{V}_{50}$ with a slightly larger difference in PEFR and smaller differences in FEV_1, Differences in $\dot{V}_{25}$, FRC and TLC do not follow any pattern.

SECTION 6

DISCUSSION

Although limited in number, studies evaluating pulmonary function during upper respiratory infection suggest a component of pulmonary involvement. Alterations in pulmonary function with either natural or experimental upper respiratory infection have been detected with dynamic measurements at elevated frequencies (1,5,4), or by measurement of closing volume (3) and CO-diffusing capacity (2). Spirometric changes have been found only with the use of a He-O_2 gas mixture in spontaneous disease (3) but routine spirometry has shown some differences after intranasal administration of influenza A vaccine (6,7). In general the changes in pulmonary function are subtle and inconsistent within and among groups, but the abnormalities detected are generally attributed to acute peripheral airways obstruction. The more pronounced effect in the presence of preexisting small airway disease supports this hypothesis (2,3,7). Our data fit this interpretation.

In the children with URI, the changes in pulmonary function parameters were not all statistically significant. However, we believe the changes were real since FVC, FEV_1, PEFR, MMEF and $\dot{V}_{50}$ decrease in all four age-sex groups: 35 percent of these changes were significant with $P \leq 0.05$; and 60 percent were significant with $P \leq 0.10$. We found a reduction in FVC without a change in TLC and a reduction of the flow rates at most lung volumes suggesting earlier airway closure. The reported small caliber of peripheral airways in young children (8) may enhance changes in pulmonary function parameters with URI. This could explain the more pronounced changes observed in the younger children. The flow rate measured at low lung volume, $\dot{V}_{25}$, which for theoretical reasons (17,18) should be most sensitive to changes in peripheral airways, was not detectably altered. However, Knudson et al. (19) in an epidemiological study showed that FEV_1 was superior to flow at low lung volume for detecting abnormalities in younger subjects.

This study also provides data to establish predictive equations for pulmonary function parameters in children younger than previously reported. In our study, we found that standing height was a more reliable predictor of pulmonary function than age, and that using both age and height provided only a slight improvement as measured by the reduction in the SEE and the SEBC. This is consistent with the finding of Dickman et al. (11) that pulmonary function parameters are most highly correlated with height. Polgar et al. (9) and Zapletal et al. (10) described a nonlinear relationship between pulmonary function parameters and height but their prediction equation spanned a wider range of heights than represented by either of the two age groups in our study population. In their recent report Knudson et al. (12) used both age and height in a regression equation but the relation-

ship was established with data from subjects over a much wider age range than is generally used. In difference to these studies, our data indicate that over a limited age range pulmonary function parameters can be related to height with a linear relationship.

The height range in our older group coincides with that of younger groups in most other studies (9-12). Regression equations for our older group fall below the mean but within $\pm$ 2 S.D. of those shown in Polgar et al. (9), which represents the compilation of all acceptable published data available at that time. Since adult blacks generally fall below the prediction curves established with a predominantly white population (20), we partially attribute our lower mean values to the large fraction of blacks in our study (66 percent).

The SEBC values represent the variability about the regression line established without including adjustments for individual variations in the analysis. These values provide confidence limits on predicted pulmonary function parameters for the general population and may be used in establishing normal ranges. Dividing the SEBC by the mean value provides a normalized estimate of the variability analogous to the coefficient of variation. For our four age-sex groups, this normalized measure of variability expressed as a percentage ranged as follows: 12 - 18 percent for FVC and FEV_1; 16 - 21 percent for PEFR; 24 - 30 percent for MMEF and $\dot{V}_{50}$; 33 - 41 percent for $\dot{V}_{25}$; 18 - 26 percent for FRC; and 10 - 13 percent for TLC. This variability appears similar to that reported by Zapletal et al. (10) and Dickman et al. (11). The variability described in the review by Polgar et al. (9) is about one-half of ours but their analysis included considerably more data.

The apparent linear relationship between the measured parameters and height suggests that pulmonary function growth--and presumably lung maturation--is simply a reflection of overall growth within relatively narrow age ranges. However, others (9-12) have found that over a more extensive age range, the relationship is clearly nonlinear. In our study the slope coefficent in the regression equation provides a measure of the relative growth of pulmonary function in our four age-sex groups. In the older group, both the actual values for the pulmonary function parameters and the slopes of the regression lines were similar for males and females. In younger females, all slopes appear to be lower than corresponding values in the other three groups. These results can be explain by hypothesizing a lower overall slope in female prior to puberty, and a rapid acceleration in pulmonary function growth near puberty. Our older female group could contain data from both the prepubertal linear growth period and the accelerated adolescent period. Since males mature later, their rapid acceleration in pulmonary function growth may not have occured in the age groups studied. As a result, the slope in the older female population would be larger than that in younger females and similar to that seen in males

In terms of growth, Zapletal et al. (10) suggested that increases in pulmonary function related to height are highly correlated with growth of TLC and that normalization of pulmonary function parameters with TLC makes them independent of height. Green et al. (21) and Black et al (22) did

not find this effect in adults. From calculations using our regression equations we found that increases in FVC, FEV_1 and PEFR appeared to be closely correlated with increases in TLC. In contrast, variations in MMEF, $\dot{V}_{50}$ and $\dot{V}_{25}$ showed less correlation with TLC suggesting that processes other than increasing TLC play a role in growth of the maximal expiratory flow.

In conclusion, we believe that reliable measurements of pulmonary function have been obtained in children over a period of several years. The data provide a basis for predicting pulmonary function parameters for children younger than previously reported. The nature of this prospective, longitudinal study made it possible to test the same children when well and at the time of intercurrent URI. These data strongly suggest pulmonary function changes in the absence of clinical evidence of lung involvement. These changes could be explained by subclinical pulmonary disease, reflex changes in peripheral airways due to upper tract inflammantion, or reduced subject effort during illness. The last possibility is considered unlikely since careful attention was given to the reproducibility of each test session. The impact of pulmonary function alterations on the growing lung cannot be assessed presently, but it appears that these abnormalities are frequent and occur with otherwise uncomplicated acute respiratory infections.

Comprehensive microbiologic and serologic studies to define the etiology of URI episodes in the study population are being analyzed and will be reported separately. Preliminary examination of the data reveals the full spectrum of common respiratory agents which have been associated with childhood URI. In addition, continued study at this population should provide data describing prospectively the growth of lung function in early childhood.

SECTION 7

STUDIES INITIATED IN TERMINAL YEAR OF GRANT

Immune responsiveness against the respiratory syncytial virus (RSV) was assessed in the study population because of increasing evidence that this agent causes repeated infections at yearly intervals. In a review of the past 10 years, Dr. Fred Henderson in our lab has documented RSV infections in 89 children occurring 176 times as demonstrated either by virus isolation (90) or seroconversion (86). In the entire population, 51 children have had from one to four reinfections. There were 61 primary RSV infections in children followed from birth, of whom 35 have had at least one recurrence. For consequative annual infections, the recurrence rate was as high as 94%.

Against this background was assessed the serum antibody response and the antigen specific reactivity of circulating thymus-derived lymphocytes. Blood samples were obtained from children in the Frank Porter Graham Day Care Center in the spring and fall of each year. Serum neutralizing antibody assay against RSV was performed by the plaque reduction method (27). Peripheral blood lymphocyte transformation was measured by tritiated thymidine incorporation after five day incubation of heparinized whole blood samples with RSV infected Hep cells as antigen or noninfected Hep cell controls. As shown in figure one, greater than 90% of children over four months of age responded to a primary RSV infection with a significant rise in the titer of serum neutralizing antibody. Within nine months there was a marked decline in the geometric mean titer. In the subsequent spring, there was another antibody titer rise following the second RSV infection in these children.

The response of circulating T-lymphocytes followed a somewhat different course as shown in figure 2. While all children demonstrated a capacity for T-cell reactivity as manifested by response to phytohemagglutinin, none of 13 children tested after primary RSV infection demonstrated antigen specific T-cell stimulation. In contrast, seven of seventeen (41%) children demonstrated a significant response following their second RSV infection.

The observations on the immune response of day care children incurring repeated infections with RSV provide data for speculation on several important points. First, it has recently been suggested that the host cell-mediated immune response (CMI) may be an important pathogenetic mechanism in RSV disease (23). This theory stems from knowledge that previous exposure to parenteral-killed RSV vaccine rendered children vulnerable to severe clinical illness upon natural infection (24). In such vaccinated children, all who were tested prior to natural infection had developed CMI as measured by circulating antigen responsive lymphocytes (25). Despite this, these children suffered more severe RSV disease than did nonvaccinated controls.

Further, there is precedence for a detrimental rate of CMI in respiratory infections through study of *M. Pneumoniae* infections in day-care children (26). This agent produces lower respiratory tract illness most commonly in school-age children and adolescents, and uncommonly in the very young child. Yet evidence now exists that asymptomatic *M. Pneumoniae* infection may be frequent in the early years of life, but only during the ages when *M. Pneumoniae* illness becomes more common do increasing numbers of children with *M. Pneumoniae* infection mainifest a positive peripheral lymphocyte response to *M. pneumoniae* antigen. In current study of the day care population, none of the children infected a single time with RSV, and less than 50% of those infected two times, developed peripherial lymphocyte reactivity to the RSV antigen. Since lymphocytes from seropositive adults manifested transformation under the same *in vitro* conditions, these negative results seem very significant. When these data are correlated with the fact that RSV illness is most prevalent among very young children, presumably after the initial RSV infection, it would seem doubtful that CMI is a crucial element in RSV disease pathogenesis.

A second important point of interest in these studies was the finding that with one exception infants and young children could mount a brisk systemic antibody response following primary RSV infection. Previous studies by Parrott et al. (27) had demonstrated that the serum complement-fixation antibody response to RSV was impaired in very young children, raising speculation that a delayed or decreased immune response could contribute to the increased severity of RSV disease during early infancy. Data from children at the day care center demonstrates a comparable serologic rise after first and second RSV infections, suggesting that at least in the age groups studied, impaired development of circulating RSV-neutralizing antibody is not a major contributor to disease pathogenesis. Of possibly more significance was the observed decline in serum antibody levels after the primary infection. Within a nine-month period, there was more than a four-fold fall in the geometric mean titer of serum-neutralizing antibody activity. In contrast to this pattern, Wright et al (28) have recently shown that seronegative children incurring influenza A infection respond with a hemagglutination inhibition antibody response which remains stable over a two-year period and correlates with complete protection against a second influenza A infection. Repeat RSV infection in the day-care population was the rule rather than the exception. Whether differences in these two respiratory viral agents is due to antigenicity, invasiveness, or differences in other aspects of the host immune response, remain important questions for future study. Of particular interest is the role of local immune antibody response. While it has been demonstrated that a significant proportion of infants and young children develop secretory antibody after natural or vaccine-induced RSV infection (23), the ability to link local respiratory tract antibody with disease resistance or to define the protective levels of antibody remain difficult because of a non-antibody inhibitor of RSV present in nasal washings of young children. This problem is being addressed in ongoing EPA supported research through development of alternative methods for measuring secretory antibody activity.

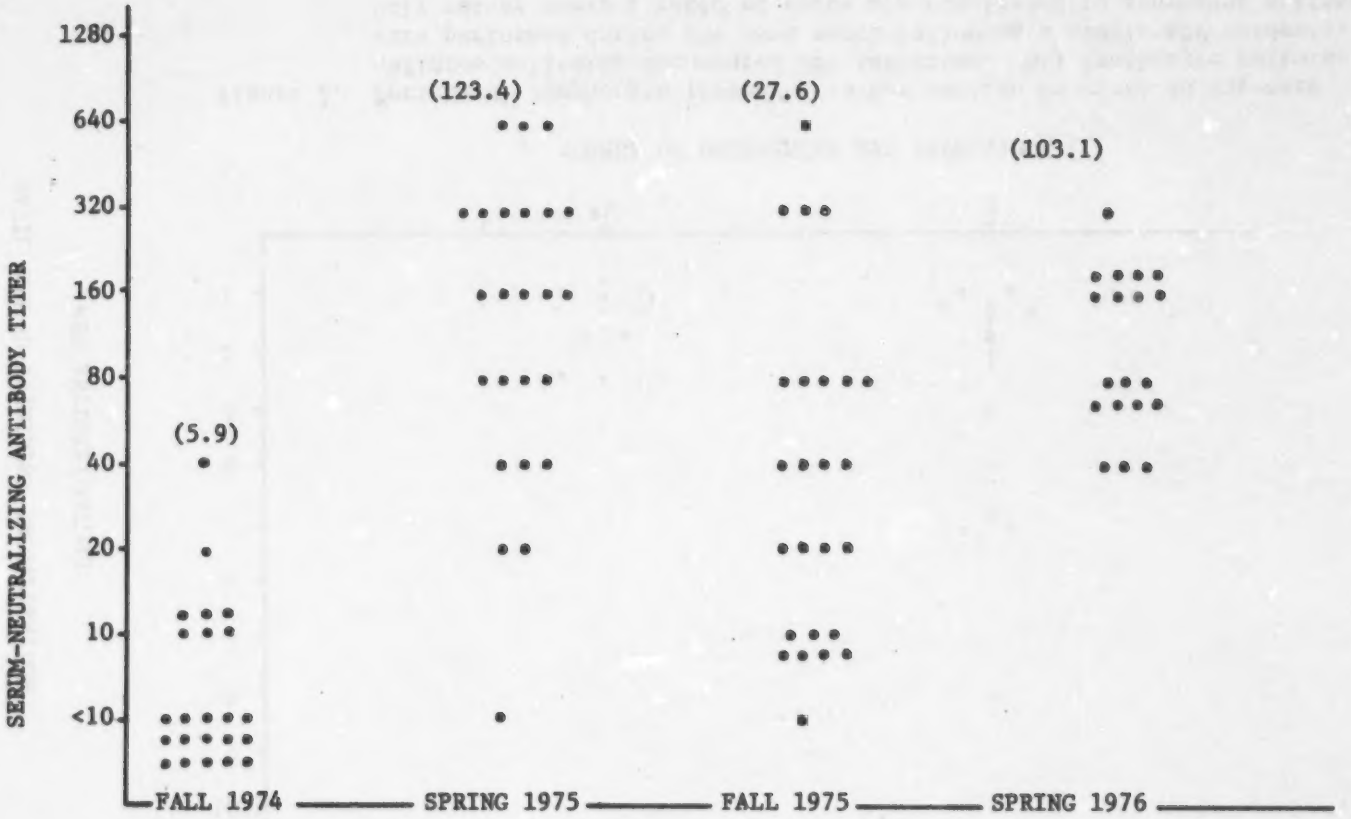

Figure 1. Serum-neutralizing antibody for RSV in day-care children observed through two wintertime RSV epidemics. Geometric mean titer in parenthesis.

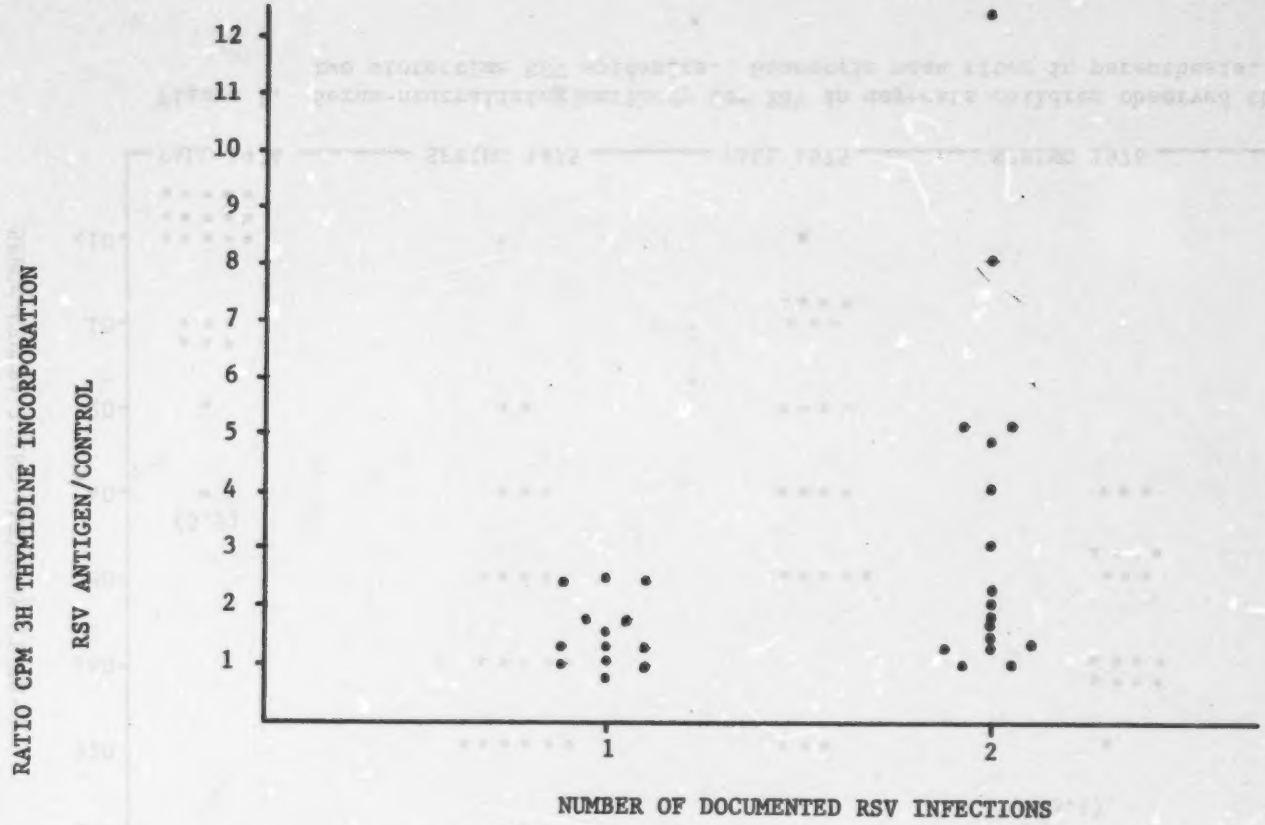

Figure 2. Peripheral lymphocyte responses to RSV antigen *in vitro* in day-care children following documented RSV infection. All lymphocyte cultures were performed during the same month following a single RSV epidemic. Only values above a ratio of three are considered to represent antigen reactivity.

TABLE 1. REPRODUCIBILITY OF SPIROMETRIC MEASUREMENTS IN CHILDREN: STANDARD ERROR OF THE ESTIMATES (SEE)* FOR FVC

Variables Included	Males <84 mo.	Males >84 mo.	Females <84 mo.	Females >84 mo.
Age and height	176	204	147	325
Height	176	208	151	325
Age	262	323	185	363

*SEE are given in milliliters.

TABLE 2. REGRESSION COEFFICIENTS USING HEIGHT AS INDEPENDENT VARIABLE

Parameter	Male* <84 mo.		Male† >84 mo.		Female** <84 mo.		Female†† >84 mo.	
	INT.	SLOPE	INT.	SLOPE	INT.	SLOPE	INT.	SLOPE
FVC (ml)	-2781	35.0	-2873	35.4	-2418	31.0	-2740	34.4
FEV_1 (ml)	-2351	30.4	-2549	31.7	-2109	27.6	-2358	30.0
PEFR (ml/s)	-5201	72.3	-4244	66.2	-4374	63.8	-6827	84.2
MMEF (ml/s)	-2154	34.5	-1984	32.8	-1792	30.6	-2574	37.3
$\dot{V}_{50}$ (ml/s)	-1704	31.9	-2179	36.4	-2835	42.0	-2805	42.0
$\dot{V}_{25}$ (ml/s)	-788	17.1	-458	13.5	-146	10.3	-527	14.1
FRC (ml)	-2864	32.8	-2425	27.9	-1869	22.5	-2696	29.0
TLC (ml)	-3712	48.6	-3372	43.9	-2508	35.5	-3665	45.3

* Based on 211 spirometric and 104 lung volume measurements in 17 subjects.

† Based on 106 spirometric and 90 lung volume measurements in 12 subjects.

** Based on 339 spirometric and 162 lung volume measurements in 29 subjects.

†† Based on 192 spirometric and 177 lung volume measurements in 15 subjects.

TABLE 3. POPULATION STATISTICS FOR SUBJECTS LESS THAN 84 MONTHS OLD

Parameters	Male (<84 mo.)*			Female (<84 mo.)†		
	Adjusted population mean	SEE	SEBC	Adjusted population mean	SEE	SEBC
FVC (ml)	1035	118	176	994	110	151
FEV_1 (ml)	962	108	168	928	108	140
PEFR (ml/s)	2648	388	492	2709	449	581
MMEF (ml/s)	1570	351	452	1629	362	465
$\dot{V}_{50}$ (ml/s)	1747	362	477	1860	417	522
$\dot{V}_{25}$ (ml/s)	1047	335	426	1031	353	414
FRC (ml)	820	175	202	769	174	196
TLC (ml)	1769	199	233	1638	165	191

(continued)

TABLE 3 (continued)

Parameters	Male (>84 mo.)**			Female (>84 mo.)††		
	Adjusted population mean	SEE	SEBC	Adjusted population mean	SEE	SEBC
FVC (ml)	1749	150	208	1770	139	325
FEV_1 (ml)	1563	151	184	1575	139	281
PEFR (ml/s)	4328	550	698	4304	529	874
MMEF (ml/s)	2260	440	544	2315	481	548
$\dot{V}_{50}$ (ml/s)	2618	504	641	2689	444	800
$\dot{V}_{25}$ (ml/s)	1262	359	415	1274	316	440
FRC (ml)	1241	169	219	1070	174	231
TLC (ml)	2367	186	240	2241	171	397

* Includes 211 spirometric and 104 lung volume measurements in 17 subjects.

† Includes 339 spirometric and 162 lung volume measurements in 29 subjects.

** Includes 106 spirometric and 90 lung volume measurements in 12 subjects.

†† Includes 192 spirometric and 177 lung volume measurements in 15 subjects.

*** SEE (standard error of the estimate) characterizes the variability about the regression line obtained by correcting for individual variation. SEBC (standard error between children) characterizes the variability about the regression line obtained without correcting for individual variations.

TABLE 4. STATISTIC SHOWING DIFFERENCE BETWEEN NORMAL AND SYMPTOMATIC SUBJECTS

Parameters	Male (<84 mo.)*				Female (<84 mo.)†			
	Normal adjusted mean	Symptomatic adjusted mean	F value	P	Normal adjusted mean	Symptomatic adjusted mean	F value	P
FVC (ml)	1051	998	9.99	.003	1014	957	17.80	.0001
FEV_1 (ml)	970	939	2.94	.088	946	895	15.23	.0001
PEFR (ml/s)	2683	2549	4.16	.043	2754	2624	5.72	.0170
MMEF (ml/s)	1573	1559	0.05	.818	1658	1575	3.57	.0600
$\dot{V}_{50}$ (ml/s)	1758	1717	0.44	.507	1903	1777	6.17	.0140
$\dot{V}_{25}$ (ml/s)	1046	1052	0.01	.906	1036	1023	0.09	.7690
FRC (ml)	812	849	0.65	.421	768	773	0.03	.8580
TLC (ml)	1759	1807	0.80	.372	1635	1645	0.11	.7410

(continued)

Table 4 (continued)

	Male (>84 mo.)**				Female (>84 mo.)††			
	Normal adjusted mean	Symptomatic adjusted mean	F value	P	Normal adjusted mean	Symptomatic adjusted mean	F value	P
FVC (ml)	1766	1691	3.39	.069	1777	1744	1.58	.2100
FEV_1 (ml)	1574	1527	1.35	.248	1575	1573	0.01	.9180
PEFR (ml/s)	4406	4063	5.28	.024	4340	4170	2.97	.0870
MMEF (ml/s)	2266	2235	0.67	.796	2348	2194	2.95	.0880
$\dot{V}_{50}$ (ml/s)	2637	2552	0.39	.536	2715	2594	2.14	.1450
$\dot{V}_{25}$ (ml/s)	1249	1302	0.35	.553	1270	1286	0.06	.8010
FRC (ml)	1234	1267	0.43	.513	1072	1063	0.06	.8130
TLC (ml)	2362	2384	0.18	.675	2254	2191	3.35	.0690

* Includes 156 spirometric and 82 lung volume measurements while asymptomatic and 55 spirometric and 22 lung volume measurements while symptomatic. Data were obtained for 17 subjects.

† Includes 222 spirometric and 113 lung volume measurements while asymptomatic and 117 spirometric and 49 lung volume measurements while symptomatic. Data were obtained from 29 subjects.

** Includes 82 spirometric and 70 lung volume measurements while asymptomatic and 24 spirometric and 20 lung volume measurements while symptomatic. Data were obtained from 12 subjects.

†† Includes 151 spirometric and 141 lung volume measurements while asymptomatic and 41 spirometric and 36 lung volume measurements while symptomatic. Data were obtained from 15 subjects.

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